CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-239

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 23, 2009
To:	Russell Katz, MD, Director Division of Neurology Products
Through:	Kellie Taylor, PharmD., MPH, Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis
From:	Felicia Duffy, RN, BSN, MSEd, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name:	Sumavel DosePro (Sumatriptan) Injection; 6 mg/0.5 mL
Application Type/Number:	NDA# 22-239
Applicant:	Zogenix
OSE RCM #:	2009-404

CONTENTS

1 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the revised container labels, carton labeling, and insert labeling submitted as part of the January 14, 2009 submission (see Appendices A through F).

2 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and carton labeling can be improved to minimize the potential for medication errors. DMEPA previously provided the Review Division with recommendations on the insert labeling in OSE review #2007-2070 dated October 20, 2008. We do not have any additional comments at this time on the insert labeling. Section 2.1 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 2.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Daniel Brounstein, OSE Project Manager, at 301-796-0674.

2.1 COMMENTS TO THE APPLICANT

A. General Comments on Container Labels and Carton Labeling

1. The presentation of the proprietary name, Sumavel DosePro, on two different lines and the use of two different colors for the proprietary name contribute to the appearance that the name is only Sumavel. Revise the proprietary name (Sumavel DosePro) so it appears in the same font and color and on the same horizontal plane, so that it is conveyed to the reader that the proprietary name is Sumavel DosePro and not solely 'Sumavel'.
2. The product strength blends in with the established name. Increase the size of the product strength to increase its prominence.

B. Carton Labeling

The teal color dominates the principle display panel of the sample 4- pack carton. Thus, the drug name, product strength, and route of administration lack prominence on the principle display panel as this information is confined to a small portion of space. Revise the principle display panel to increase the prominence of the proprietary name, established name, product strength, and route of administration.

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/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 15, 2009
To:	Russell Katz, M.D., Division Director
	Division of Neurology Products
Through:	Jodi Duckhorn, MA, Team Leader
	Division of Risk Management
From:	LaShawn Griffiths, MSHS-PH, BSN, RN
	Patient Product Information Reviewer
	Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Patient Package Insert and Patient Instructions for Use)
Drug Name(s):	Sumavel DosePro (sumatriptan) injection
Application Type/Number:	NDA 22-239
Applicant/sponsor:	Zogenix, Incorporated
OSE RCM #:	2008-1361

1 INTRODUCTION

Zogenix Inc. submitted a New Drug Application (NDA 22-239) for Intraject Sumatriptan (sumatriptan succinate), 6 mg. on December 28, 2007. Intraject Sumatriptan (sumatriptan succinate) is a needle free drug device indicated for the acute treatment of migraine and cluster headaches.

The Division of Neurology Products requested that the Division of Risk Management's Patient Labeling and Education Team review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU). This review is written in response to that request.

2 MATERIAL REVIEWED

- Sumavel DosePro Patient Package Insert (PPI) submitted December 28, 2007
- Sumavel DosePro Patient Instructions for Use (IFU) submitted December 28, 2007
- Sumavel DosePro Prescribing Information (PI) submitted December 28, 2007 and revised by the Review Division throughout the current review cycle

3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the Applicant with our recommended changes are indicated in section 4 below.

In our review of the PPI and IFU, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI and IFU. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI and IFU. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI and IFU.

4 CONCLUSIONS AND RECOMMENDATIONS

The proposed PPI and IFU were reviewed as separate documents because the proposed IFU was in PDF, the Applicant should put them back together for labeling and dissemination.

Sumavel DosePro (sumatriptan injection) Patient Package Insert (PPI)

1. The Applican't proposed PPI has the following readability scores:
    - Flesch Reading Ease: 42.7%
    - Flesch-Kincaid Grade Level: 10.8

    The sponsor's readability scores for the PPI are higher than that recommended for optimal patient comprehension. We recommend that the sponsor simplify the PPI by incorporating our recommendations.

    Our revised PPI has the following readability scores:
    - Flesch Reading Ease: 53.8%
    - Flesch-Kincaid Grade Level: 8.9

2. We deleted the sections (b) (4) The purpose of Patient Information is to enhance appropriate use and to provide important information to patients about medications. This disease specific information can be placed at the end of the PPI after the "Ingredients" section or preferably addressed with the patient separately from the product specific information.
3. The medications (b) (4) have been deleted from the "Who should not take" section because these medications have been discontinued.
4. In the section "What should I tell my healthcare provider before taking Sumavel DosePro?" the term "overweight" is vague the Applicant should quantify an amount of what is considered to be "overweight".
5. In the section "What are the possible side effects of Sumavel DosePro", the Applicant should:
    - clarify for the patient where the "feeling of heaviness" is located
    - clarify for the patient where the "pressure sensation" is located
    - clarify what "feeling strange" means
    - specify where the muscle pain is located, for example, near the injection site or all over the body?
6. We have added the following statement to the end of the section, "What are the possible side effects of Sumavel DosePro?":

    Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This verbatim statement is required for all Medication Guides effective January 2008. [1] Although not required for voluntary PPIs like Sumavel DosePro, we recommend adding this language to all FDA-approved patient labeling for consistency.

Sumavel DosePro (sumatriptan injection) Instructions for Use (IFU)

1. The Applicant's proposed IFU has the following readability scores:
    - Flesch Reading Ease: 75.6
    - Flesch-Kincaid Grade Level: 5.8

    The Applicant's readability scores for the IFU are acceptable.

2. The Applicant should use at least a 10 point font throughout the text. The font in the instructions for use that was sent to the Agency for review is very small and hard to read.
3. We recommend adding an illustration labeling all the parts of the Sumavel Dosepro.
4. Do not use all capital letters in patient information. For better comprehension and to call attention to important information, use other techniques such as bolded font or text boxes.
5. The terms (b) (4) have been removed. This over simplifies the steps needed to use the device.
6. The Applicant's illustration of the Sumavel DosePro pen does not list a "tip" as one of the parts of the device. The Applicant should label the illustration showing/naming the "tip".
7. Do not use italics in patient information.
8. In the "press" section the Applicant should clarify if the device needs to stay against the skin for a specific amount of time before removing to ensure that the dose has been delivered?

Please let us know if you have any questions.

[1] 21 CFR 208.20 (b)(7)(iii)

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/s/

LaShawn Griffiths
6/15/2009 01:57:44 PM
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Jodi Duckhorn
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Maternal Health Team Review

Date: April 20, 2009 **Date Consulted:** March 20, 2009

From: Jeanine Best, MSN, RN, PNP
Regulatory and Labeling Reviewer, Pediatric and Maternal Health Staff

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, M.D.
Associate Director, Pediatric and Maternal Health Staff

To: Division of Neurological Products

Drug: Sumavel™ DosePro™ (sumatriptan injection) needle-free delivery system 6 mg

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Sumavel™ DosePro™ labeling, NDA 22-239, dated January 14, 2009

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of Sumavel™ DosePro™ labeling.

INTRODUCTION

Zogeniz Inc. submitted an original NDA 22-239 on December 28, 2007 for Sumavel™ DosePro™ (sumatriptan injection) needle-free delivery system 6 mg, for the acute treatment of migraine attacks with or without aura and the acute treatment of cluster headache episodes. Sumatriptan is a Serotonin 5-hydroxytriptamine or 5-HT agonist that binds to serotonin receptors and causes vasoconstriction and neuronal inhibition as the mechanism of action thought to alleviate migraine and cluster headaches. The Division of Neurology products (DNP) issued a Complete Response (CR) Letter on October 31, 2009, due to the presence of genotoxic impurities in the clinical drug product. Zogeniz submitted a Class 1 Resubmission on January 14, 2009, in response to the October 31, 2008, CR Letter. This NDA is a 505(b)(2) submission with Imitrex® (sumatriptan) Injection, 6mg/0.5/mL (GlaxoSmithKline) listed as the reference listed drug. The Maternal Health Team (MHT) notes that GlaxoSmithKline (GSK) established a voluntary pregnancy registry for sumatriptan and now contracts with Kendal International Inc. for pregnancy registry responsibilities for its two sumatriptan-containing products, Imitrex® and Treximet®. Zogeniz Inc. has not proposed a pregnancy registry for Sumavel™ DosePro™.

MHT has been consulted to review the pregnancy and Nursing Mothers section of Sumavel™ DosePro™ labeling.

BACKGROUND

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

5 HT_1 Pregnancy Registries

Migraine headaches disproportionately affect women, and in particular, women of childbearing age and potential. The prevalence of migraine in women is approximately 18 % verses 6% in men, with the highest prevalence occurring between ages 25 and 55 years.[1] In addition, migraines occur in pregnant women, and untreated migraines can lead to adverse effects on both the pregnant woman and to the fetus. Effective migraine treatments that are safe and effective for both the pregnant women and fetus are necessary.

A pregnancy registry is a prospective, observational cohort study that enrolls pregnant women before pregnancy outcomes are known and documents maternal, fetal, and neonatal

[1] Lipton R, Bigal M. The epidemiology of migraine. Amer J Med. 2005:Mar;118 Suppl 1:3S-10S

outcomes following drug exposure in-utero. Two triptan manufacturers established voluntary pregnancy registries as part of their epidemiologic safety monitoring programs at the time of product approval (GlaxoSmithKine for sumatriptan and naratriptan and Merck & Co. for rizatriptan). GlaxoSmithKline (GSK) later contracted with Kendle International Inc. to manage a combined pregnancy registry for sumatriptan (Imitrex® and Treximet®) and naratriptan (Amerge®). Pregnancy registries have not been established, nor requested by FDA, for the other approved 5-HT_1 agonists (almotriptan, eletriptan, frovatriptan, and zolmitriptan); however, Section 901 of FDAAA (effective March 25, 2008), created section 505(o) of the Act, which authorizes FDA to require postmarketing studies or clinical trials at the time of approval to assess signals of serious risk related to the use of the drug (one of three stated purposes).[2] In addition, Section 905 grants FDA the authority and responsibility to develop postmarketing approaches to studying drug safety in populations, such as pregnant women, when the population is understudied prior to drug approval and when routine pharmacovigilance and adverse event reporting are not expected to adequately capture this data. Under FDAAA, a review division can require a pregnancy registry as a condition of approval – a postmarketing requirement (PMR).

To date, the limited pregnancy registry data (mainly first trimester exposure) with sumatriptan and to a lesser extent with naratriptan and rizatriptan, show no significant outcome differences for congenital malformations or poor pregnancy outcomes when compared with background rates in the general population or observed rates in controls subjects. There is very limited registry data on pregnancy exposure in the second and third trimesters with sumatriptan, naratriptan, and rizatriptan.[3] In addition, the two 5-HT_1 pregnancy registries do not collect identical patient data.

This review provides MHT's suggested revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Sumavel™ DosePro™ labeling as well as ensuring that the pregnancy and nursing information in the FDA-approved patient labeling is consistent with the information presented in the Professional Information (PI). In addition, MHT provides a recommendation for a Pregnancy Registry for Sumavel™ DosePro™

SUMBMITTED LABELING
Sponsors Proposed Pregnancy and Nursing Mothers Labeling

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/s/

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LABELING REVIEWER

Karen Feibus
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MEDICAL OFFICER
I agree with the content and recommendations contained in this review

Lisa Mathis
4/21/2009 02:14:48 PM
MEDICAL OFFICER

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-239
APPLICANT	Zogenix, Incorporated
DRUG NAME	Sumavel DosePro (sumatriptan injection)
SUBMISSION DATE	(Request Received from DNP March 10, 2009
SEALD REVIEW DATE	March 20, 2009
SEALD REVIEWER(S)	Jeanne M. Delasko, RN, MS

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SEALD comments sent to review division (DNP) 03-20-2009.

Laurie Burke
3/23/2009 06:32:36 PM
INTERDISCIPLINARY

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	October 20, 2008
To:	Russell Katz, MD, Director Division of Neurology Products
Through:	Kellie Taylor, PharmD, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Felicia Duffy, RN, BSN, MSEd, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Sumatriptan Labeling Review and Usability
Drug Name(s):	Sumavel DosePro (Sumatriptan) Injection
Submission Number:	N/A
Application Type/Number:	NDA 22-239
Applicant:	Zogenix
OSE RCM #:	2007-1964 and 2007-2070

CONTENTS

EXECUTIVE SUMMARY

DMEPA reviewed the carton and container labels, insert labeling, usability studies, and postmarketing data for sumatriptan and identified areas of improvement that may minimize the potential for medication errors with Sumavel DosePro (sumatriptan) injection.

Although the usability study subjects reported ease of use and clear instructions for Sumavel DosePro, as with any device, we anticipate errors either related to the device or user error.

DMEPA recommends label and labeling revisions to improve the readability of the proprietary name, established name, and product strength and to increase the prominence of pertinent information on the container labels and carton labeling of Sumavel DosePro, and to further enhance the clarity of the package insert labeling and in the instructions for use. For full recommendations, we refer you to section 5 of this review.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Neurology Products to evaluate the container label, carton and insert labeling, patient package insert labeling, patient instructions for use for Sumavel DosePro (sumatriptan) injection. Additionally, the Applicant submitted usability studies associated with the patient instructions for use.

1.2 REGULATORY HISTORY

Sumatriptan is currently available as a nasal spray, as tablets, and as an injectable marketed by Glaxo Smith Kline with the proprietary name, Imitrex and Imitrex STATdose. The injectable formulation of Imitrex was initially approved in 1992 supplied in a vial. Imitrex STATDose was approved in 1996 as 6 mg prefilled cartridges, and in 2006, the 4 mg prefilled cartridges were approved.

1.3 PRODUCT INFORMATION

Sumavel DosePro is a New Drug Application indicated for the acute treatment of migraine attacks with or without aura, and the acute treatment of cluster headache episodes. Sumavel DosePro contains the active ingredient, sumatriptan, in a needleless delivery system in which injections are administered subcutaneously into the abdomen or thigh. It is not designed for administration in other body parts, including the arm. Sumavel DosePro is supplied as a prefilled, single-dose, needleless delivery system delivering 0.5 mL of solution containing 6 mg of sumatriptan. Single subcutaneous doses should not exceed 6 mg, and no more than two 6 mg doses should be given in 24 hours, separated by at least 1 hour.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA medication error staff to conduct a label, labeling, and/or packaging risk assessment. Additionally, usability studies in association with the patient package insert, and patient instructions for use were submitted by the Applicant.

The primary focus of the assessments is to identify and remedy potential sources of medication errors. DMEPA defines a medication error as any preventable event that may cause or lead to

inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

Since the active ingredient of the proposed product (sumatriptan) is currently marketed, the Division of Medication Error Prevention and Analysis conducted a search of the FDA Adverse Event Reporting System (AERS) for all postmarketing safety reports of medication errors with sumatriptan. AERS was searched using the trade name "Imitrex%", verbatim substance "Imitrex%", and active ingredient "sumatriptan". The MedDRA terms used were the High Level Group Term "Medication Errors" and the Preferred Term "Pharmaceutical Product Complaint".

The cases were manually reviewed to determine if a medication error occurred. Those cases that did not describe a medication error were excluded from further analysis as well as cases involving oral Imitrex. The cases that did describe a medication error were categorized by type of error. DMEPA reviewed the cases within each category to identify factors that contributed to the medication errors.

2.2 USABILITY STUDIES

The Applicant submitted two clinical usability studies on the proper use of the drug delivery system. These two studies (ARMD-02A00-0204) and (ZX000-0702) were conducted to investigate the adequacy of the design of the drug delivery system, the instructions for use, and the appropriateness of the training material for the correct use of Sumavel DosePro. The Applicant also conducted a third usability study to assess the usability of Sumavel DosePro by patients during acute migraine attacks, to evaluate the reasons for incorrect use of Sumavel DosePro during acute migraine attacks, to evaluate the adequacy of instructional materials, and to evaluate the frequency of occurrence and persistence of local injection site reactions (bleeding, swelling, erythema, and bruising (ZX001-0701). DMEPA reviewed these studies to determine what type of medication errors occurred during the study, and what the Applicant did in order to mitigate the errors that occurred. We also evaluated the usability studies to determine if the medication errors were mitigated as a result of revised labeling and/or device.

2.3 LABELS AND LABELING

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

Because the medication error staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The medication error staff uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on December 28, 2007, the following labels and insert labeling for the medication error staff to review (see Appendices A though E for images):

- Container Label
    - Sample and Dispensing
- Carton Labeling
    - Sample Single Unit
    - Sample 4-Pack
    - Dispensing Single Pack
    - Dispensing 6-Pack
- Prescribing Information (no image)

3 RESULTS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

A total of 480 cases involving sumatriptan were retrieved on August 20, 2008. After manual review of the cases, 117 cases were determined to be relevant to the review of this sumatriptan product. The majority of the remaining 363 cases involved lack of effect of sumatriptan, intentional misuse/overdose, and adverse events. Table 1 below describes the types of errors in which the relevant cases were categorized. These errors will undergo full evaluation in the Imitrex/Imitrex STATdose (sumatriptan injection) postmarketing review (OSE review #2007-2326).

Table 1: Sumatriptan medication errors categorized by type

Medication errors pertinent to this review	
Type of Error	**# of Cases (n=117)**
Device issues	60
Wrong route of administration	41
Wrong technique	9
Wrong site of injection (needlesticks)	7

The contributing factors that were included in some of the reports relevant to this review were indicated in the narratives or noted in review of the cases. They are described in detail below.

3.1.1 Device issues (n=60):

These errors include medication errors that occurred with the Imitrex STATdose device. These errors can be broken down into these three major categories: 1) device malfunctions, 2) defective device and 3) difficulty with the device.

Device malfunctions (n=31) were described as the pen jamming, pen misfiring, cartridge came out of device, plunger button stuck, injector spring fell apart, and pen would not inject. In one case where the device misfired (ISR #5638500-9), a caregiver was sprayed in the eye and experienced burning and redness. Other outcomes included lack of effect (as a result of not receiving medication), puncture wound, accidental injection, bruising, and a broken needle requiring surgical removal.

The defective device cases (n=25) can be attributed to factors such as bent needles, broken needles, no needle in cartridge, defective spring, device fell apart, broken cartridge, and the needle not coming down when triggered. The main results of a defective device was reported as lack of effect due to the user not receiving the medication as a result of the defective device or bruising/injection site pain due to a bent needle.

Reporters also had difficulty with the pen device (n=4) including difficulty with loading the pen, difficulty with pushing the button on the pen, difficulty with pushing the plunger, and difficulty with assembling the pen. In one case, as a result of difficulty with loading the pen and getting it to release correctly, which resulted in the patient developing convulsions, nausea, and vomiting. As a result the patient was hospitalized.

3.1.2 Wrong route of administration (n=41):

A total of 41 medication errors involved the wrong route of administration. Twenty-seven cases involved intravenous administration rather than subcutaneous administration (n=27). Some reports indicate that some patients were administered Imitrex STATdose intravenously while hospitalized. The reports did not indicate the contributing factors. Patient outcomes included prolonged hospitalization, coma, hospitalization, cerebral bleed, chest pain, tingling, elevated blood pressure, and dizziness.

Ten (n=10) cases described sumatriptan administered intramuscularly. Some cases occurred in the inpatient setting. In one specific case a nurse drew Imitrex STATdose into syringe because he/she did not have an Imitrex STATdose pen. Other contributing factors were not reported. The outcomes reported were injection site necrosis, muscle tightness, and bruising.

There were two cases of oral administration (n=2). One patient self-administered sumatriptan by placing it under his tongue. Another case indicated that the patient took the injection orally and it made her nauseous. There were no contributing factors described in either of these reports.

The remaining two cases (n=2) described the wrong route of administration, but did not specify the route.

3.1.3 Wrong technique (n=9):

There were a total of nine cases (n=9) related to the wrong technique for Imitrex STATdose. The description of errors are as follows: cartridge not loaded correctly, used Q-tip to inject medicine from cartridge without using the injector pen, injecting without a cartridge, failure to prime the pen, didn't understand loading instructions thus used a tuberculin syringe, released the medication into the air after loading cartridges, administered dose with a plunger from a regular syringe, medication shot into the air, and injecting with an empty cartridge.

One of the nine cases described a mother preparing the sumatriptan pen and the medication shot into the air and landed in the child's mouth. The child subsequently developed welts on her back which turned into blisters. In two other cases the contributing factors were described as not understanding loading instructions and failure to properly follow directions. In one case a patient experienced lack of effect; the outcome was not reported in the remaining eight cases.

3.1.4 Wrong site of injection (n=7):

A total of seven cases (n=7) describe the wrong site of injection (needlesticks). The breakdown of cases is as follows: needlestick into thumb (n=2), hand (n=2), finger (n=2) and unspecified site (n=1). Two needle sticks occurred as a result of the device misfiring. One needle stick occurred as a result of the device flying into the air after a nurse was startled after the device misfired. One case indicated that the patient couldn't get the device to work. Patient outcomes include swelling, erythema, bleeding, HIV prophylaxis, and bruising.

3.2 USABILITY STUDIES

The Applicant conducted three usability studies. In the first two studies, subjects performed simulated injections into a foam pad. The objective of these studies was to evaluate the ability of subjects to appropriately use the injector device. The first study (ARMD 02-A00-0204) was conducted with 102 naïve healthy subjects. As a result of the first usability study, the instructions for use were revised. The revised instructions for use were then used for the second usability study (ZX000-0702) which contained 20 migraineurs. The user instructions were once again revised based on the results from the second study. The third usability study was conducted with 52 migraineurs who actually injected themselves with the drug product during a migraine attack.

3.2.1 Usability Study ARMD 02A00-0204

This is the first usability study. ARMD 02A00-0204 contained 102 naïve healthy subjects. Three subjects oriented the device incorrectly, and two subjects injected themselves into their thumb or index finger as they appeared to be unaware that they had pointed the injection end of device in the wrong direction after it was enabled. To mitigate the possibility of incorrect orientation, alerts were added to the user instructions and on the device (the latter taking the form of an arrow on the underside of the lever, which becomes visible once the lever is properly rotated). Ninety-three (93%) percent of naïve users on their first attempt were able to successfully perform a simulated injection. After viewing a video demonstration, the proportion of successful injections increased to 97% upon the second attempt. Overall, for both attempts at injection, 98% of subjects either agreed or strongly agreed that the device was easy to use. Ninety percent (90%) of subjects agreed or strongly agreed that the user instructions were clear and easy to understand.

3.2.2 Usability Study ZX000-0702

This study was conducted after usability study ARMD 02A00-0204. In the pilot usability study containing 20 migraineurs (ZX000-0702), no subjects incorrectly oriented the device, and no subjects injected themselves into their thumb or index finger. As a result of this study, the instructions for use were revised a total of three times, once at the beginning of the study prior to review by any subject, once as a result of the findings from Part 1 of the study, and then a final revision based on findings from Part 2 of the study. The mean score for overall ease of use using only the printed instructions was high at 6.37 using a 1 to 7 Likert scale with 1 being "Strongly Disagree" and 7 being "Strongly Agree". The clarity of instructions had a mean rating of 6.21 on the same scale.

3.2.3 Usability Study ZX001-0701

Clinical usability study (ZX001-0701) resulted in 98% of subjects using Sumavel DosePro correctly on their first use during an acute migraine attack outside the clinic. Nearly all reported uses, 97%, of Sumavel DosePro were performed correctly (122/125 usability assessments). Three incorrect uses in three separate subjects were reported, each attributed to a different causative factor. One subject failed to press the device straight down against the skin until the

burst of air was heard. However, the subject used the device correctly in subsequent uses. The second subject felt that the device "bounced off her leg", and the third subject indicated that they "did not receive medication" and used another device. In 124 of 125 reported uses of Sumavel DosePro, 99% of subjects somewhat agreed, agreed or strongly agreed that "The… instructional materials provided were adequate; meaning they were clear and easy to follow." One subject did self-inject into their arm, however, the subject indicated that they were instructed to do so by the site study staff.

3.3 CONTAINER LABEL AND CARTON LABELING

Upon review of the container labels and carton labeling, we note that the proprietary and established names and product strength are difficult to read due to the light colored font in which they are presented. Additionally, the product strength is difficult to locate due to the small font size.

The proposed proprietary name is a two-part name: Sumavel DosePro. We note that the second portion of the proprietary name "DosePro" appears above the first portion of the name.

The route of administration statement is lacking from the principle display panel.

3.3.1 Container Label

The NDC number does not appear in the top third portion of the principle display panel.

3.3.2 Carton Labeling

The NDC number does not appear on the top third portion of the principle display panel on the sample 4-pack display carton.

The NDC number is not prominent and is difficult to read.

The principle display panel of the sample single-pack and dispensing single-pack cartons appear cluttered.

The net quantity volume is not identified.

3.4 PACKAGE INSERT

The Dosage and Administration section is confusing as the first paragraph is wordy. This section should clearly state to deliver 6 mg of Sumavel DosePro subcutaneously.

The expression of strength in the Dosage and Administration section (6 mg/0.5 mL) is not consistent with the expression of strength on the carton labeling and container labels (6 mg).

3.5 PATIENT PACKAGE INSERT

No comment.

3.6 INSTRUCTIONS FOR USE

The usability studies have identified items of information that appear confusing. This includes lack of information or unclear information. The following items are noted:

- The instruction in the first paragraph of Step 2 is unclear.
- The instruction in the second paragraph of Step 3 is unclear.
- The statement in Step 3 that indicates a dose has been delivered is not clearly highlighted.

- The instructions do not instruct the user to discard the device after its single use.

4 DISCUSSION

Upon review of the usability studies, AERS cases, and labels and labeling, DMEPA identified several areas of risk that we believe the Applicant can improve upon and help to minimize through labeling prior to approval.

First, the AERS cases identified failures with a product containing the same active ingredient in a needled injection device. These failures include: device malfunction/device failure, wrong route of administration, wrong technique, and wrong site of injection. With the exception of errors related to the wrong injection route of administration, the same failures relate to this new needless device. We acknowledge that usability studies tested the clarity of the instructions for use and the ability for subjects to use the device correctly, and that were made to this device and the labeling as a result of the usability studies. However, based upon our evaluation and assessment of postmarketing medication errors captured in the AERS database, we believe that the proposed device remains vulnerable to device malfunctioning issues, wrong route of administration (unrelated to injection), wrong technique and wrong site of injection.

4.1 USABILITY STUDIES

The Applicant provides five potential advantages of the needle-free device over the current needle-based device including: 1) ease of administration without the need for drug preparation, 2) elimination or reduction of apprehension in individuals who have a needle fear or phobia, 3) elimination of needle stick injuries, 4) improvement in patient compliance and/or adherence, and 5) increased likelihood of self-administration. The areas we are most concerned with from a safe use perspective are the elimination of needlestick injuries and that patients can follow instructions to use the device appropriately.

In both the naïve user usability study (ARMD 02A00-0204) and the pilot usability study (ZX000-0702), subjects simulated self-injections into a foam pad held against their abdomen. The naïve user usability study resulted in 3 subjects orienting the device incorrectly, and 2 of those subjects injected themselves in either the thumb or finger. As a result of the study subjects' feedback, modifications were made to the user instructions and device. Additionally, subjects reported that the icons on the device were unnoticeable because of their small size and low contrast against the handle. It may be useful to highlight the icons in a different color in order to help the user differentiate the steps involved in priming the device and delivering the dose. In the pilot usability studies, no subjects incorrectly handled/oriented the device, or injected themselves in the thumb or finger. The user instructions were revised a total of three times as a result of both usability studies. In both studies, subjects indicated that the most difficult step was step 1, breaking off the snap-off tip because of the fear or apprehension that they would break the device. It appears that the user instructions were adequately revised to reflect that force may be needed to snap off the tip, which may lessen the fear of breaking the device.

In the clinical usability study, subjects used Sumavel DosePro during an acute migraine outside the clinic. Fifty-one of 52 subjects used the device correctly on their first use during and acute migraine, and the majority of subjects agreed that the instructional materials provided were clear and easy to follow. We acknowledge that the Applicant made adjustments to the user instructions and device based on the results of the studies. However, we believe that additional revisions to the user instructions can be made in order to further clarify and simplify the use of the product. Clarifying the wording in step 2 and step 3 of the user instructions may further increase correct use of the device.

4.2 AERS CASES

When evaluating the AERS cases, we identified the following types of errors relevant to this product: Device issues resulting in injection failure, wrong route of administration, wrong technique, and wrong site of injection. Although the wrong site of injection cases were mainly needlesticks, cases in the usability study in which patient oriented the device incorrectly and injected the wrong site demonstrate that the wrong site of injection is possible with the needless system.

4.2.1 Device Issues

The errors that occurred with Imitrex STATdose were divided into three main categories: device malfunction, defective device, and difficulty with the device. As with any device the potential exists for malfunctions to occur such as the device jamming or misfiring. Although neither of these types of malfunctions occurred in the usability studies, the potential still exists for these types of errors to occur with Sumavel DosePro. However, the types of error described as the cartridge coming out or the injector spring falling apart are less likely to occur with Sumavel DosePro because this device does not need to be assembled by the user, as opposed to Imitrex STATdose. Additionally, there are fewer steps with the use of Sumavel DosePro in comparison with the number and complexity of steps involved with Imitrex STATdose.

The majority of the defective device cases with Imitrex STATdose pertained to issues with the needle. It is highly unlikely that there will be cases related to needles because Sumavel DosePro is a needle-free system. There were also cases of difficulty with the device related to difficulty assembling the device, and pushing the button or plunger. Sumavel DosePro is a single-unit device that does not require assembly by the user. Thus, the anticipation of medication errors as a result of assembly is minimal. The usability studies did not indicate that users had difficulty with the device; however, some users did indicate that some older patients with dexterity issues may experience some difficulty manipulating the device.

4.2.2 Wrong Route of Administration

The wrong route of administration occurred in 42 cases with Imitrex STATdose. Because Sumavel DosePro is a needle-free system, it would seem less likely that the drug could be inadvertently delivered intravenously or intramuscularly. According to the Applicant Sumavel DosePro has been designed to deliver sumatriptan subcutaneously. The cases related to the oral administration of sumatriptan were primarily due to users intentionally dosing themselves in this manner. Oral dosing with Imitrex STATdose may be more accessible due to the availability of a needle which would more easily facilitate oral administration of the drug. However, the lack of a needle on Sumavel DosePro may help to deter improper oral use of the product. Additionally, the usability studies did not result in any wrong route of administration errors.

4.2.3 Wrong Technique

The cases of wrong technique primarily pertained to the assembly of Imitrex STATdose or confusion with the instructions. Because Sumavel DosePro does not require assembly, we do not anticipate the same type of wrong technique errors as seen with Imitrex STATdose. With regard to confusion with the instructions, we are satisfied that this potential risk has been mitigated since the majority of subjects in the usability studies indicated that the instructions for use were clear and easy to follow.

4.2.4 Wrong Site of Injection (needlesticks)

There were seven cases of needle sticks with Imitrex STATdose. Although Sumavel DosePro is a needle-free device, two subjects in the usability studies did inject themselves in the finger/thumb. As a result of the wrong site of injection, the user instructions were revised in order to mitigate the potential for this type of error. Despite these modifications, we believe there is still some risk of this occurrence instructions are not closely attended to and since this type of error is inherent to the design of the device. . However, we are satisfied that the sponsor's revisions have adequately addressed this risk since there were no additional reports of wrong site of injection into the thumb/finger/hand in the usability studies.

4.3 CONTAINER LABEL AND CARTON LABELING

When evaluating the container label and carton labeling, we note some areas that make the labels vulnerable to error. The first area of concern is the presentation of the proprietary name, established name, and product strength. They all are difficult to read because of poor color contrast between lettering (font color green) and the background (also green) which decreases readability. Additionally, the product strength is difficult to locate on the label because it lacks prominence. It is important for patients and practitioners to be able to clearly identify the proprietary name, established name, and strength of a drug product, therefore, these items should be clearly legible.

The second area of concern is that the second portion of the name "DosePro" appears above the first portion of the name "Sumavel". This could be misleading because it may appear that the proprietary name is "DosePro Sumavel" rather than Sumavel DosePro, as people are used to reading from top to bottom, left to right. If the name is misread as such, it could potentially be mis-shelved by pharmacy staff. This could potentially lead to shelf selection errors.

Additionally, the route of administration does not appear on the container label, which is not in accordance with 21 CFR 201.100(b)(3). Since this product is not administered orally, the route of administration must be present on the labels and labeling.

4.3.1 Container Label

The NDC number does not appear in the top third of the principle display panel, instead it appears on the side panel beneath the bar-code. If the Applicant wishes to include the NDC number in association with the bar-code, it must be done so in accordance with 21 CFR 207.35(3)(i). Otherwise, it is difficult to locate the NDC number. Improvements can be made to the readability of the label if the manufacturer information and PN number is relocated to the side panel to allow room for the NDC number at the top third of the label.

4.3.2 Carton Labeling

On the sample 4-pack display carton, the NDC number does not appear in the top third of the principle display panel, instead it appears on bottom flap. This is not in accordance with 21 CFR 207.35(3)(i). Additionally, the NDC number appears very small and is difficult to locate.

Once "DosePro" is relocated to appear on the same plane as "Sumavel", the principle display panels of the sample single-pack and dispensing single-pack cartons will appear cluttered. Because of the small nature of the carton, only pertinent information (e.g., proprietary name, established name, strength, route of administration, NDC number, net quantity, Rx only statement) should appear on the principle display panel in order increase the readability of the labeling and to minimize the potential for confusion and error. The statement "See full prescribing information for dosage and administration and instructions for use" is not an essential

statement that must appear on the principle display panel. Relocating the statement would allow more room for increasing the prominence of more other information.

The volume of the net quantity is not presented on the principle display panel. Although the strength is expressed in milligrams, Sumavel DosePro is an injectable solution where the volume to be injected should be indicated on the carton labeling.

4.3.3 Package Insert

The first three sentences in the Dosage and Administration (D&A) section are confusing and may lead to error because they are wordy and not as clear and concise as the information presented in the D&A section on page 1 of the "Highlights of Prescribing Information". It is confusing to initially read, "One Sumavel DosePro is the maximum single recommended dose," and in the next sentence read, "The maximum recommended dose that may be given in 24 hours…." This may confuse the reader as to what is the maximum recommended dose. Providing the specific dose first and then the supplemental information may be less confusing for the user.

Additionally, the recommended dose is expressed as 6 mg/0.5 mL, which is not consistent with the expression of strength in the "Highlights" section or on the carton labeling and container labels. This should be consistent in order to minimize confusion and error.

4.3.4 Instructions for Use

The usability studies showed that some of the users were confused or failed at step 2 and step 3. DMEPA discussed our concerns with DRISK and DRISK will address DMEPA's concerns in OSE review #2008-1361. We refer the Applicant to OSE DRISK review #2008-1361 for recommended revisions.

5 CONCLUSIONS AND RECOMMENDATIONS

DMEPA recommends the label and labeling recommendations outlined below be implemented to improve the readability of the proprietary name, established name, and product strength and to increase the prominence of pertinent information on the container labels and carton labeling of Sumavel DosePro, and to further enhance the clarity of the package insert labeling and in the instructions for use.

5.1 COMMENTS TO THE DIVISION

DMEPA would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed.

Based upon our assessment of the labels and labeling, and usability studies, we have identified areas needed of improvement.

Please copy DMEPA on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Daniel Brounstein, Project Manager, at 301-796-0674.

5.1.1 Instructions for Use

1. Refer to OSE DRISK review #2008-1361 for revisions to Step 2 and Step 3 to enhance clarity.

2. Include in the Instructions for Use, information that instructs the patient to discard the device after use.

We have provided recommendations in section 5.2 and request this information be forwarded to the Applicant.

5.2 COMMENTS TO THE APPLICANT

DMEPA recommends the label and labeling recommendations outlined below be implemented to improve the readability of the proprietary name, established name, and product strength and to increase the prominence of pertinent information on the container labels and carton labeling of Sumavel DosePro, and to further enhance the clarity of the package insert labeling and in the instructions for use.

Although the usability study subjects reported ease of use and clear instructions for Sumavel DosePro, as with any device, we anticipate errors either related to the device or user error.

Based upon our assessment of the labels and labeling, and usability studies, DMEPA has identified areas of needed improvement. We have the following recommendations below.

5.2.1 Container Label and Carton Labeling

1. Provide better color contrast with the background of the label for the font used to display the proprietary name, established name, and product strength.
2. Increase the prominence of the product strength. Revise the product strength to include the volume in each injection (e.g., 6 mg/0.5 mL).
3. Relocate "DosePro" so it appears immediately following "Sumavel" in order to minimize confusion that the proprietary name is Sumavel DosePro rather than "DosePro Sumavel".
4. Include the route of administration statement "For Subcutaneous Use Only" on the principle display panel.

5.2.1.1 Container Label

1. Relocate the NDC number to the top third of the principle display panel in accordance with 21 CFR 207.35(3)(i).

5.2.1.2 Carton Labeling

1. On the sample 4-pack display carton, relocate the NDC number to the top third of the principle display panel in accordance with 21 CFR 207.35(3)(i) and increase the prominence of the NDC number.
2. Relocate the "See full prescribing information…." statement to the side panel.
3. Include the volume in the net quantity of the carton (e.g., 1 prefilled, 0.5 mL single-dose unit)

5.2.2 Package Insert

1. Revise the first paragraph in the Dosage and Administration section to use the same wording provided in the Dosage and Administration section in the Highlights section on

the first page of the package insert. This wording is more concise, and less confusing than the current working in Dosage and Administration.

3 pages of draft labeling withheld immediately after this page as B4 (TS/CCI)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kellie Taylor
10/19/2008 06:38:38 PM
DRUG SAFETY OFFICE REVIEWER
signing on behalf of F. Duffy and D. Toyer

Denise Toyer
10/20/2008 12:35:09 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/20/2008 04:10:33 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 15, 2008

FROM: Hyojong Kwon, Ph.D.
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Yau 10/15/2008
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 22-239,
Sumatriptan Intraject, Sponsored by Zogenix, Inc.

TO: Russel Katz, M.D.
Director
Division of Neurology products (DNP)

At the request of DNP, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study:

Study Number: ZX001-601

Study Title: "A Randomized, Open-Label, Single-Dose, Four-way Crossover Study to Evaluate the Pharmacokinetic and Bioequivalence of Sumatriptan Delivered via the Intraject® System Versus the IMITREX STAT dose System® at Three Injection Sites in Healthy Adult Subjects"

The clinical and analytical portions of the study were conducted at Covance Global Clinical Research Unit, Inc., Dallas, TX and [redacted] respectively.

Following the inspections at Covance Clinical Research Unit, Inc. (6/16-19) and at [redacted] Forms 483 were issued. The objectionable items and our evaluation of them follow:

Clinical Site: Covance Clinical Research Unit, Dallas, Texas

Clinical observations for Study ZX001-0601:

1. Informed consent was not properly documented in that the written informed consent used in the study was not signed by the suject or the subject's legally authorized representative at the time of conesent. No documentation for 18 out of 57 subjects signed the 12/12/06 revised consent.

The revised consent form requires the completion of 'Fitzpatrick skin typing assessment' to meet the inclusion criteria. Although all the subjects completed this protocol-required test, it is objectionable that the firm failed to assure that proper informed consent was obtained.

2. Subjects 1053 and 2042 had received the last dose on the previous trial, 6 days before receiving the first dose on the following trial when 30 days were required between trials.

The deviation is reported in the submission. The impact of the above protocol deviation (item 2) for subjects 1053 and 2042 needs to be considered.

Analytical Site: [redacted]

Analytical observations for Study ZX001-0601:

3. Failure to document all study data in the final bioanalytical report.

The "analytical reassay summary" table reported that 5 original samples from subject 1009 were reassayed because the original results were above the upper quantitation limit. However, at the sponsor's request, all samples from the duplicate set (i.e., the plasma samples were split into two aliquots at the clinical site) for this subject were additionally reassayed without being reported (attachment 1). This reassay confirmed the original data, and ruled out the sponsor's speculation that the high concentrations found in the 5 original samples resulted from sample contamination. There was no documentation at the analytical site to indicate contamination from another source (e.g. sample handling at the clinical site). Thus, the data from

the subject 1009 were excluded from PK analysis without justification and there was no further evaluation or investigation of this issue in the sponsor's NDA submission.

4. Failure to use freshly prepared calibration standards in the freeze/thaw stability and sample processing stability in the validation study.

Although the firm's experimental designs for freeze/thaw was not optimal, there was no significant impact on the accuracy of the data. Because one cycle freeze/thaw (F/T) stability was supported by the long-term stability data and all the samples were analyzed after one F/T cycle, except for 5 samples of subject 1009. These 5 samples were reassayed but the accuracy of the data was confirmed by assaying a duplicate set. Sample-processing stability was not properly evaluated, however, there was no significant impact on the accuracy of the data because the runs were processed immediately after samples being extracted.

5. Failure to be consistent with the SOP for accepting/reporting reassay results.

The firm stated that the period 1 samples for subject 1042 were reassayed to investigate possible mislabeling of period 1 samples between subjects 1042 and 2042. The firm stated that the reassayed data for subject 1042 were reported because they confirmed the original data. The original data for subject 1042 should be included in PK analysis.

Conclusion:

The Division of Scientific Investigations recommends the following:

- The reviewer needs to consider the impact of the above protocol deviation (item 2) for subjects 1053 and 2042.
- The data from 5 samples of subject 1009 (3m, 6m, 9m, 20m, 30m of 3d and phase 3) should not be excluded from PK analysis based on possible sample contamination during bioanalytical analysis, since this possibility was eliminated (item 3).

- The reviewer should consider the original data set (item 5) for the period 1 of subject 1042 during PK analysis.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Hyojong Kwon 10/15/2008

Hyojong Kwon, Ph.D.

Final Classifications:

VAI: Covance Clinical Research Unit, Dallas, Texas
VAI: [redacted]

cc:
OC DSI/RF
OC DSI/Oshaughnessy
OC DSI/Kwon/CF
OND/ODEI/DNP/Chen/Bastings
HFR-CE8585
Draft: HK 10/05/08
Edits: JAO10/06/08
DSI: [redacted]; O:\BE\EIRCOVER\2239cov.sum.doc
FACTS: [redacted]

Attachment 1

Original 5 samples

Sample ID	Calculated Concentration (ng/mL)	Dilution Factor	Accuracy (%)	Use Record	Sample Comment	Sample Annotation
S1009 D3 H0 M3 P3 X:Sumatriptan	741.	1.00	N/A	none		AL
S1009 D3 H0 M6 P3 X:Sumatriptan	837.	1.00	N/A	none		AL
S1009 D3 H0 M9 P3 X:Sumatriptan	520.	1.00	N/A	none		AL
S1009 D3 H0 M12 P3 X:Sumatriptan	70.5	1.00	N/A	none		
S1009 D3 H0 M15 P3 X:Sumatriptan	68.4	1.00	N/A	none		
S1009 D3 H0 M20 P3 X:Sumatriptan	524.	1.00	N/A	none		AL
S1009 D3 H0 M30 P3 X:Sumatriptan	319.	1.00	N/A	none		AL

(AL: Above the upper limit of quantitation)

Reassayed 5 samples (after dilution)

Sample Name	Sample ID	Calculated Concentration (ng/mL)	Dilution Factor
MB-1218563-1-1-C	S1009 D3 H0 M0 P3 X:Sumatriptan	0.00633	1.00
MB-1218563-1-2-C	S1009 D3 H0 M0 P3 X:Sumatriptan	< 0	1.00
MB-1218564-1-1-C	S1009 D3 H0 M3 P3 X:Sumatriptan	798	10.0
MB-1218564-1-2-C	S1009 D3 H0 M3 P3 X:Sumatriptan	806.	10.0
MB-1218565-1-1-C	S1009 D3 H0 M6 P3 X:Sumatriptan	855.	10.0
MB-1218565-1-2-C	S1009 D3 H0 M6 P3 X:Sumatriptan	854.	10.0
MB-1218566-1-1-C	S1009 D3 H0 M9 P3 X:Sumatriptan	514.	10.0
MB-1218566-1-2-C	S1009 D3 H0 M9 P3 X:Sumatriptan	511.	10.0
MB-1218567-1-1-C	S1009 D3 H0 M12 P3 X:Sumatriptan	64.6	1.00
MB-1218567-1-2-C	S1009 D3 H0 M12 P3 X:Sumatriptan	65.6	1.00
MB-1218568-1-1-C	S1009 D3 H0 M15 P3 X:Sumatriptan	65.3	1.00
MB-1218568-1-2-C	S1009 D3 H0 M15 P3 X:Sumatriptan	67.7	1.00
MB-1218569-1-1-C	S1009 D3 H0 M20 P3 X:Sumatriptan	536	10.0
MB-1218569-1-2-C	S1009 D3 H0 M20 P3 X:Sumatriptan	514	10.0
MB-1218570-1-1-C	S1009 D3 H0 M30 P3 X:Sumatriptan	313.	10.0
MB-1218570-1-2-C	S1009 D3 H0 M30 P3 X:Sumatriptan	324.	10.0

Duplicate samples

Sample Name	Sample ID	Calculated Concentration (ng/mL)	Dilution Factor
MB-1218571-1-1-C	S1009 D3 H1 M0 P3 X Sumatriptan	54.7	1.00
MB-1218571-1-2-C	S1009 D3 H1 M0 P3 X Sumatriptan	56.7	1.00
MB-1218572-1-1-C	S1009 D3 H1.5 M0 P3 X Sumatriptan	28.4	1.00
MB-1218572-1-2-C	S1009 D3 H1.5 M0 P3 X Sumatriptan	28.6	1.00
MB-1218573-1-1-C	S1009 D3 H2 M0 P3 X Sumatriptan	8.50	1.00
MB-1218573-1-2-C	S1009 D3 H2 M0 P3 X Sumatriptan	8.49	1.00
MB-1218574-1-1-C	S1009 D3 H3 M0 P3 X Sumatriptan	5.05	1.00
MB-1218574-1-2-C	S1009 D3 H3 M0 P3 X Sumatriptan	5.22	1.00
MB-1218575-1-1-C	S1009 D3 H4 M0 P3 X Sumatriptan	3.73	1.00
MB-1218575-1-2-C	S1009 D3 H4 M0 P3 X Sumatriptan	3.79	1.00
MB-1218576-1-1-C	S1009 D3 H6 M0 P3 X Sumatriptan	1.45	1.00
MB-1218576-1-2-C	S1009 D3 H6 M0 P3 X Sumatriptan	1.44	1.00
MB-1218577-1-1-C	S1009 D3 H8 M0 P3 X Sumatriptan	0.795	1.00
MB-1218577-1-2-C	S1009 D3 H8 M0 P3 X Sumatriptan	0.788	1.00
MB-1218578-1-1-C	S1009 D3 H10 M0 P3 X Sumatriptan	0.631	1.00
MB-1218578-1-2-C	S1009 D3 H10 M0 P3 X Sumatriptan	0.661	1.00
MB-1218564-1-3-C	S1009 D3 H0 M3 P3 X Sumatriptan	757.	1.00
MB-1218564-1-4-C	S1009 D3 H0 M3 P3 X Sumatriptan	760.	1.00
MB-1218565-1-3-C	S1009 D3 H0 M6 P3 X Sumatriptan	809.	1.00
MB-1218565-1-4-C	S1009 D3 H0 M6 P3 X Sumatriptan	812.	1.00
MB-1218566-1-3-C	S1009 D3 H0 M9 P3 X Sumatriptan	506.	1.00
MB-1218566-1-4-C	S1009 D3 H0 M9 P3 X Sumatriptan	505.	1.00
MB-1218569-1-3-C	S1009 D3 H0 M20 P3 X Sumatriptan	509.	1.00
MB-1218569-1-4-C	S1009 D3 H0 M20 P3 X Sumatriptan	505.	1.00
MB-1218570-1-3-C	S1009 D3 H0 M30 P3 X Sumatriptan	303.	1.00
MB-1218570-1-4-C	S1009 D3 H0 M30 P3 X Sumatriptan	310.	1.00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hyojong Kwon
10/15/2008 10:14:48 AM
BIOPHARMACEUTICS
Dr. Martin Yau (acting for Dr.Viswanathan) signed the paper copy on 10/15/2008

From: Burdick, William M.
Sent: Thursday, September 25, 2008 4:00 PM
To: Claffey, David
Cc: Burdick, William M.
Subject: RE: cdrh

Attached is my review, David.

Bill

C O N S U L T R E V I E W

Date: September 25, 2008

From: William M. Burdick, Biomedical Engineer/Physicist
ODE/DAGID, General Hospital Device Branch

To: David J. Caffey, Ph.D., Chemist
CDER/ONDQA

Subject: SUMAVEL™ DosePro™ Pre-filled Pen Injector, mfrd. by Zoegenix, Inc.: **Engineering Review**

The subject device is a nonpyrogenic, sterilized, single-use, pre-filled pen injector intended to deliver a subcutaneous 6 mg/0.5 mL aqueous dose of sumatriptan succinate for the acute treatment of migraine attacks with or without aura and for the acute treatment of cluster headache episodes.

I was solicited to perform an engineering type of consult in order to assess the mechanical and performance characteristics of the subject device. After perusing the documents submitted by Zoegenix , the MDF, and your chemistry review memo, I realized that you had already successfully covered all the engineering and device issues as delineated below:

- The material composition, drug/material compatibility, and biocompatibility of this drug/device combination were thoroughly reviewed, assessed, and determined to be acceptable.

- The method of sterilization was verified and validated and the nonpyrogenicity information submitted was assessed and found acceptable.

- The risk management plan, including a Hazard Analysis and two FMEAs, submitted by the sponsor were evaluated and determined as appropriate.

- Mechanical and performance testing that included drop testing, vibration and shock testing, operation at temperature extremes (5 and 30 degrees C), noise emission, reliability, leakage testing, dosage accuracy, and user handling studies were effectively evaluated and found acceptable.

RECOMMENDATION
The SUMAVEL™ DosePro™ Pre-filled Pen Injector was appropriately evaluated by you concerning typical engineering and device-related issues, and results supported the acceptability of the device for its intended use. I am in complete agreement with your assessment.

William M. Burdick

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/s/

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9/29/2008 02:20:18 PM
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9/29/2008 03:20:35 PM
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